Claims

1. Transferrin, albumin and polyethylene glycol conjugates, obtainable by coupling a derivatized cytostatic compound, consisting of the cytostatic compound and a spacer molecule having a maleinimide group, to thiolated transferrin or albumin having on the average from 1 to 30 HS groups or to polyethylene glycol having, at least, one HS or H_2N group and having a mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol,
or by coupling a derivatized cytostatic compound, consisting of the cytostatic compound and a spacer molecule having a N-hydroxysuccinimide ester group, to thiolated transferrin or albumin having on the average form 1 to 30 HS groups or to the polyethylene glycol having, at least, one HO- or H_2N- group and having a mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol,
or obtainable by loading thiolated albumin with from 2 to 30 equivalents of the derivatized cytostatic compound, consisting of the cytostatic compound and a spacer molecule having a maleinimide group, and conjugating with transferrin or a monoclonal antibody which is directed against a tumor-associated antigen, via a bismaleinimide compound.

2. Transferrin, albumin and polyethylene glycol conjugates according to claim 1, obtainable by coupling a derivatized cytostatic compound, consisting of a cytostatic compound from the group of the anthracyclines, the nitrogen mustard gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the taxoids, the camptothecines, the podophyllotoxin derivatives, the vinca alkaloids or the *cis*-configured platinum(II)-complexes, respectively, and a spacer molecule having a maleinimide group, to thiolated transferrin or albumin having on the

average from 1 to 30 HS groups or to polyethylene glycol having, at least, one HS or H_2N group and having a mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol,

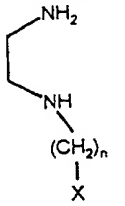
or by coupling a derivatized cytostatic compound, consisting of the cytostatic compound from the group of the anthracyclines, the nitrogen mustard gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the taxoids, the camptothecines, the podophyllotoxin derivatives, the vincan alkaloids or the *cis*-configured platinum(II)-complexes and a spacer molecule having a N-hydroxysuccinimide ester group, to thiolated transferrin or albumin having on the average from 1 to 30 HS groups or to the polyethylene glycol having, at least, one HO- or H_2N- group and having a mass of about between 5,000 and 200,000 Da, wherein about form 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol,

or by loading thiolated albumin with from 2 to 30 equivalents of the derivatized cytostatic compound, consisting of the cytostatic compound from the group of the anthracyclines, the nitrogen mustard gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the taxoids, the camptothecines, the podophyllotoxin derivatives, the vinca alkaloids or the *cis*-configured platinum(II)-complexes, respectively, and a spacer molecule having a maleinimide group, and conjugating with transferrin or a monoclonal antibody, which is directed against a tumor-associated antigen, via a bismaleinimide compound.

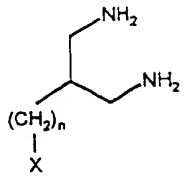
3. Transferrin, albumin and polyethylene glycol conjugates, according to anyone of the preceding claims, obtainable by reacting

a). doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxandrone, chloroambucil, melphalan, 5-fluorouracil, 5'-desoxy-5-fluorouridine, thioguanine, methotrexate, paclitaxel, docetaxel, topotecane, 9-aminocamptothecine, etoposide, teniposide, mitopodoside, vinblastine, vincristine, vindesine, vinorelbine or a compound of the general formula I, II, III or IV:

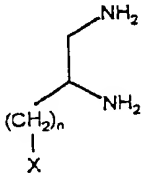
Formula I



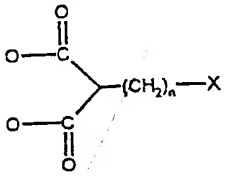
Formula II



Formula III



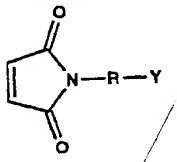
Formula IV



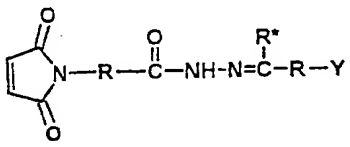
n = 0 – 6, X = $-NH_2$, -OH, -COOH, -O-CO-R-COR*, -NH-CO-R-COR*, wherein R is an aliphatic carbon chain with 1 – 6 carbon atoms or a substituted or unsubstituted phenylene group and R* is H, phenyl, alkyl with 1 – 6 carbon atoms, and the amine functions are provided with a protective group such as the *tert.*-butyloxycarbonyl protective group,

with a maleinimide compound of the general formula V, VI or VII

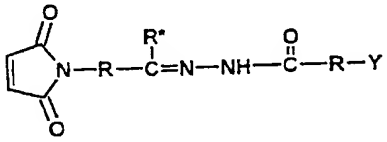
Formula V



Formula VI



Formula VII

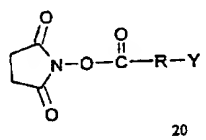


wherein, in the case that R is an aliphatic carbon chain with 1 – 6 carbon atoms, Y = -OH, -COOH, -COCl, $-CONH-(CH_2)_n-OH$, $-COO-(CH_2)_n-NH_2$, $-COO-(CH_2)_n-NHNH_2$, $-SO_3H$, $-SO_3Cl$, $-SO_2-NHNH_2$, -O-COCl, -CHO, COR* with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms, and wherein, in the case that R

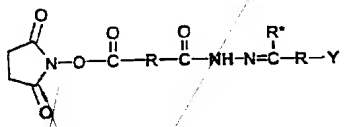
is a substituted or unsubstituted benzyl group or a substituted or unsubstituted phenylene group, Y = -OH, -COOH, -COCl, -CONH-$(CH_2)_n$-OH, -COO-$(CH_2)_n$-NH_2, -COO-$(CH_2)_n$-$NHNH_2$, -SO_3H, -SO_3Cl, -SO_2-$NHNH_2$, -O-COCl, -CHO, -COR*, -CO-$NHNH_2$ with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms,

or with an N-hydroxysuccinimide compound of the general formula VIII, IX or X

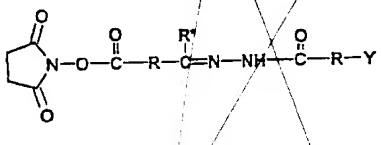
Formula VIII



Formula IX:



Formula X



wherein R is a substituted or unsubstituted phenylene group, Y = -OH, - NH_2, - $NHNH_2$, -COOH, -COCl, -COO-$(CH_2)_n$-OH, -CONH-$(CH_2)_n$-NH_2, -COO-$(CH_2)_n$-$NHNH_2$, -SO_3H, -SO_3Cl, -SO_2-$NHNH_2$, -O-COCl, -CHO, -COR*, -CO-$NHNH_2$ with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms,

wherein, in the derivatives obtained from the compounds of the general formula I, II or III, the protective group is removed and the thus-obtained amines are reacted with a tetrachloroplatinate salt to yield the corresponding *cis*-configured platinum(II)-complexes, and wherein the derivatives obtained from the compounds of the general formula IV are reacted with *cis*-[PtA_2B] (A = halogen, B = $(NH_3)_2$, ethylene diamine, propane diamine, 1,2-diaminocyclohexane) to yield the corresponding platinum(II)-complexes,

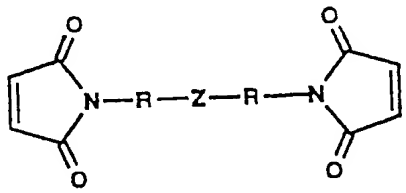
so that maleinimide derivatives or N-hydroxysuccinimide ester derivatives of cytostatic compounds are provided, wherein the chemical linkage occurs between

the cytostatic compound and the maleinimide compound or N-hydroxysuccinimide compound, respectively, through an amide, ester, imine, hydrazone, carboxylhydrazone, oxycarbonyl, acetal or ketal bond, and

b). the thus-obtained maleinimide derivative is coupled to thiolated transferrin or albumin with on the average from 1 to 30 HS groups or to polyethylene glycol having, at least, one HS- or H_2N group and having a mass of between about 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the maleinimide derivatives obtained in Step a) are bound to one molecule of transferrin, albumin or polyethylene glycol,

or the thus-obtained N-hydroxysuccinimide ester derivative is coupled to transferrin or albumin or to polyethylene glycol having, at least, one HO- or H_2N group, having a mass of between approximately 5,000 and 200,000 Da, wherein about 1 to 30 molecules of the N-hydroxysuccinimide derivatives obtained in Step a) are bound to one molecule of transferrin, albumin or polyethylene glycol,

or by loading thiolated albumin with from 2 to 30 equivalents of the maleinimide derivatives obtained in Step a) and conjugating with transferrin or a monoclonal antibody which is directed against a tumor-associated antigen, via a bismaleinimide compound of the general formula XI

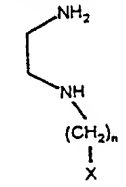


Z = -CO-NH-$(CH_2)_n$-NH-CO-, -CO-O-$(CH_2)_n$-O-CO-, -C=NH-$(CH_2)_n$-NH=C-, -C=N-NH-$(CH_2)_n$-NH-N=C-, -C=N-NH-CO-$(CH_2)_n$-CO-NH-N=C-, n = 2 – 12.

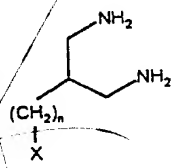
4. Method for the production of transferrin, albumin and polyethylene glycol conjugate, according to anyone of the preceding claims, characterized in that

a). doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxandrone, chloroambucil, melphalan, 5-fluorouracyl, 5'-desoxy-5-fluorouridine, thioguanine, methotrexate, paclitaxel, docetaxel, topotecane, 9-aminocamptothecine, etoposide, teniposide, mitopodoside, vinblastine, vincristine, vindesine, vinorelbine or a compound of general the formula I, II, III or IV:

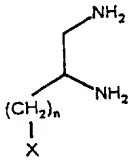
Formula I



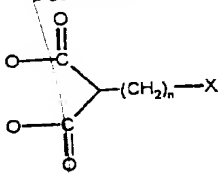
Formula II



Formula III



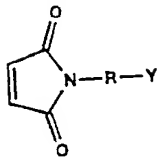
Formula IV



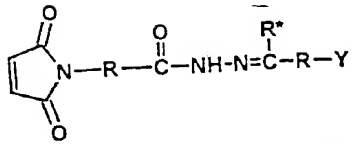
n = 0 – 6, X = $-NH_2$, -OH, -COOH, -O-CO-R-COR*, -NH-CO-R-COR*, wherein R is an aliphatic carbon chain with 1 – 6 carbon atoms or a substituted or unsubstituted phenylene group and R* is H, phenyl, alkyl with 1 – 6 carbon atoms, and the amine functions are provided with a protective group such as the *tert.*-butyloxycarbonyl protective group,

with a maleinimide compound of the general formula V, VI or VII

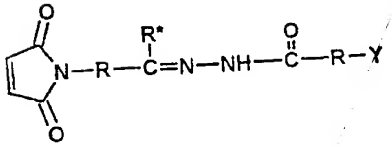
Formula V



Formula VI



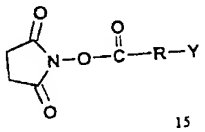
Formula VII



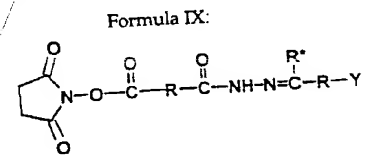
wherein, in the case that R is an aliphatic carbon chain with 1 – 6 carbon atoms, Y = -OH, -COOH, -COCl, -CONH-$(CH_2)_n$-OH, -COO-$(CH_2)_n$-NH_2, -COO-$(CH_2)_n$-$NHNH_2$, -SO_3H, -SO_3Cl, -SO_2-$NHNH_2$, -O-COCl, -CHO, -COR* with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms, and wherein, in the case that R is a substituted or unsubstituted benzyl group or a substituted or unsubstituted phenylene group, Y = -OH, -COOH, -COCl, -CONH-$(CH_2)_n$-OH, -COO-$(CH_2)_n$-NH_2, -COO-$(CH_2)_n$-$NHNH_2$, -SO_3H, -SO_3Cl, -SO_2-$NHNH_2$, -O-COCl, -CHO, -COR* with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms,

or with an N-hydroxysuccinimide compound of the general formulas VIII, IX or X

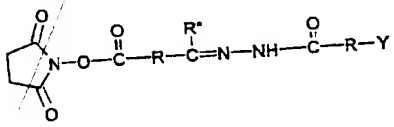
Formula VIII



Formula IX:



Formula X



$NHNH_2$, $-SO_3H$, $-SO_3Cl$, $-SO_2-NHNH_2$, -O-COCl, -CHO, -COR*, $-CO-NHNH_2$ with n = 1 – 6 and R* = H, phenyl, alkyl with 1 – 6 carbon atoms,

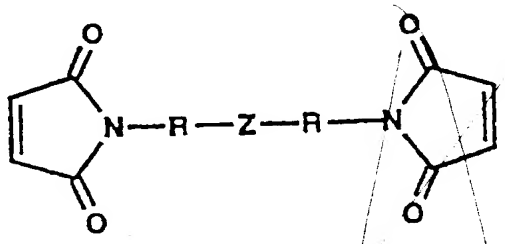
wherein, in the derivatives obtained from the compounds of the general formula I, II or III, the protective group is removed and the thus-obtained amines are reacted with a tetrachloroplatinate salt to yield the corresponding *cis*-configured platinum(II)-complexes, and wherein the derivatives obtained from the compounds of the general formula IV are reacted with *cis*-$[PtA_2B]$ (A = halogen, B = $(NH_3)_2$, ethylene diamine, propane diamine, 1,2-diaminocyclohexane) to yield the corresponding platinum(II)-complexes,

so that maleinimide derivatives or N-hydroxysuccinimide ester derivatives of cytostatic compounds are provided, wherein the chemical linkage occurs between the cytostatic compound and the maleinimide compound or N-hydroxysuccinimide compound through an amide, ester, imine, hydrazone, carboxylhydrazone, oxycarbonyl, acetal or ketal bond, and

b.) the thus-obtained maleinimide derivative is coupled to thiolated transferrin or albumin having from 1 to 30 HS groups on the average or to polyethylene glycol having, at least, one HS- or H_2N group and having a mass of between about 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the maleinimide derivatives obtained in Step a) are bound to one molecule of transferrin, albumin or polyethylene glycol,

or the thus-obtained N-hydroxysuccinimide ester derivative is coupled to transferrin or albumin or to polyethylene glycol having, at least, one HO- or H_2N group, having a mass of between approximately 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the N-hydroxysuccinimide derivatives obtained in Step a) are bound to one molecule of transferrin, albumin or polyethylene glycol,

or by loading thiolated albumin with from 2 to 30 equivalents of the maleinimide derivatives obtained in Step a) and conjugating with transferrin or a monoclonal antibody which is directed against a tumor-associated antigen, via a bismaleinimide compound of the general formula XI



Z = -CO-NH-$(CH_2)_n$-NH-CO-, -CO-O-$(CH_2)_n$-O-CO-, -C=NH-$(CH_2)_n$-NH=C-, -C=N-NH-$(CH_2)_n$-NH-N=C-, -C=N-NH-CO-$(CH_2)_n$-CO-NH-N=C-, n = 2 – 12.

5. Pharmaceutical composition containing a compound according to anyone of the claims 1 to 3 optionally together with usual carriers and auxiliary agents.

6. Use of the transferrin, albumin and polyethylene glycol conjugates according to anyone of the claims 1 to 3 for the treatment of cancer diseases.